TOBACCO INDUSTRY RESEARCH COMMITTEE
350 FIFTH AVENUE NEW YORK 1, N. Y.

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Application For Research Grant

Date: April 28, 1955

1. Name of Investigator: Janet Travell, M.D.

2. Title: Associate Professor of Clinical Pharmacology

3. Institution & Address: Cornell University Medical College
1300 York Avenue
New York 21, New York

4. Project or Subject: Electrocardiographic Effects of Nicotine in the Rabbit with Experimental Coronary Atherosclerosis.

5. Detailed Plan of Procedure (Use reverse side if additional space is needed):

Using a special test animal, we propose to determine whether nicotine injected intravenously produces electrocardiographic effects characteristic of coronary insufficiency.

Coronary atherosclerosis will be produced in male rabbits by feeding a high cholesterol diet. Controls will be fed the same basic stock diet without cholesterol. In such cholesterol-fed rabbits, we have observed the development of occlusive coronary atherosclerosis in from 3 to 5 months, as indicated by ergonovine-induced electrocardiographic changes and pathologic study of the heart (Rinzler, S.H., Travell, J. and Karp, D.: Detection of Coronary Atherosclerosis in the Living Animal by the Ergonovine Stress Test. Science, in press 1955)

The ergonovine stress test will be used to detect the presence of coronary atherosclerosis in the living rabbit. The procedure is currently as follows: With the animal under nembutal anesthesia (15 to 20 mg. Kg.). two control electrocardiograms are taken with the Sanborn Twin-Beam Cardiograph, using Leads II and V_4 and paper speeds of 25 and 75 mm./sec. Ergonovine maleate (0.05 mg. Kg.) is injected intravenously, and Leads II and V_4 are repeated after 1,3,5,10 and 15 to 20 minutes. Positivity of the test is indicated by S-T segment depression of 0.5 mm. or more. When spontaneous S-T segment depression is present in the control electrocardiogram before ergonovine, positivity is indicated by further depression of this segment. The time-sequence of events suggests that these changes are the result of myocardial ischemia secondary to coronary vasoconstriction.

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Although nicotine increases the heart rate in many species, preliminary experiments indicate that in the rabbit suitable doses of nicotine do not produce a tachycardia. This is important since a drug-induced tachycardia may interfere with the interpretation of electrocardiographic changes in the S-T segment and T waves.

If a coronary vasoconstrictor action of nicotine is demonstrated, antagonistic and synergistic actions of nicotine with other coronary vasoconstrictor and vasodilator drugs, such as vasopressin and nitroglycerin will be investigated. It has been reported that nicotine may exert effects on the coronary circulation through stimulation of the posterior pituitary gland and release of vasopressor hormones. It is anticipated that during the course of this investigation, new data will be accumulated with reference to the action on the coronary circulation of such drugs as vasopressin and oxytocin.

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6. Budget Plan:

Salaries	Full-time Research Assistant and Part-time Laboratory man	$5,200.
Expendable Supplies		800.
Permanent Equipment	Includes Twin-beam Sanborn Electrocardiograph @table $1600	1,900
Overhead		810.
Other	Pathology	200.
	Total	$8,910.

7. Anticipated Duration of Work:

July 1, 1955 to June 30, 1956

8. Facilities and Staff Available:

The usual facilities of the Department of ~~Em~~ Pharmacology. Seymour H. Rinzler, M.D. and Dorothy Karp, Ph.D., will be available for research assistance on ~~x~~ this project.

9. Additional Requirements:

This part of th investigation should be completed in one year. However, we expect to derive new ~~leads~~ leads that may deserve further study.

10. Additional Information (Including relation of work to other projects and other sources of supply):

The study concerning the ~~detection~~ detection of coronary atherosclerosis in the living animal was carried our under a grant from the National Heart Institute, National Institutes of Health, Public Health Services. Continuing support for studies on the role of the skeletal muscles in cardiovascular disease, in the amount of $6,000 annually has been committed for two more years.

Signature _____
Director of Project James Gravell, M.D.

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Business Officer of Institution

Dean, Cornell University Medical College

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